White Paper

TRUTH OR DARE

The Ten Smart Questions You Must Ask to be Successful in Assessing Commercial Drug Opportunities

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Have you ever played "Truth or Dare?" The first player asks "truth or dare?" If the second player says "truth," the first player asks a question, usually risky. If they reply "dare," the questioner asks them to do something, also usually risky. In drug development, biotech and pharmaceutical companies alike play this game internally every day. Do we move this product into Phase III? How much is this market segment really worth? Will physicians use this product and, if so, how? Are the clinical endpoints meaningful enough for physicians to use the product vs. another standard of care? Will it be reimbursed? And no senior manager wants to take the risk of not having answers to these questions in front of the FDA, the Pharmacy and Therapeutics Committee (P&T), a payor or even senior management.

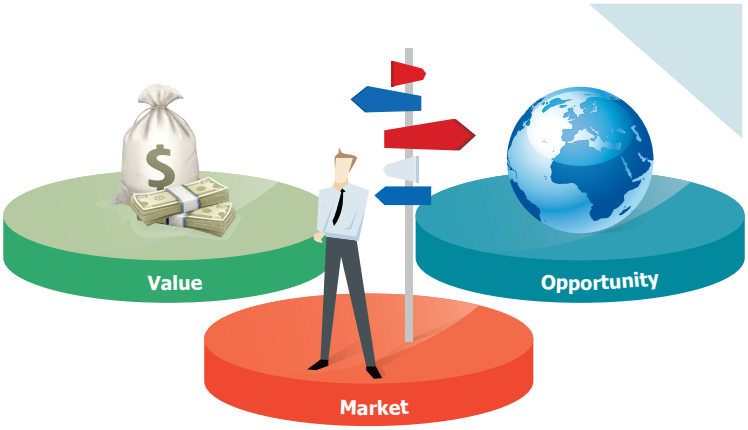
All these questions need to be answered in a world of limited resources. No pharma company, no matter what its size, has an infinite amount of money and resources to stream all its potential assets through its pipeline. For individual compounds under development, the challenge is to identify early assets that will fail so resources can be reallocated as quickly as possible. For an entire portfolio, whether it is for a specific therapeutic area or an entire company, managers need to understand how their decisions to invest in one product versus another affect risk and value.

Time and again, companies ask these questions internally, and, frequently, the answers are inadequate and, when confronted by the CEO, insufficient to inspire confidence to allocate significant resources. For them, the game is real. There are patients waiting, stockholders looking for investment returns, colleagues rooting for success and payrolls to be met.

Even for drugs that work, the challenge is to answer all the necessary questions to gain the human and financial resources that keep a project moving forward as well as answer all the necessary constituencies. No one gets a perfect SAT score here. No one has the time and the staff to even list them all, let alone, answer them all.

When topics range from epidemiology to disease characteristics to treatment algorithms to perceptions by physicians and payors, the ability to assemble, synthesize and develop critical observations and insights can challenge the skills of any Merit Scholar or experienced executive.

What makes this effort even more challenging is the silo-ed nature of many companies. To answer these questions, it is necessary to reach across and within different organizations and functions to get the answers. Have you ever seen a research scientist play "Truth or Dare" with a marketing person? It is an awkward scene to watch.



To assist companies with the kinds of analyses that help understand the Opportunity, the Market and the Value, at SmartAnalyst, we have developed 10 Smart Questions that must be asked to truly understand opportunities from a 360-degree perspective.

The Opportunity

In the beginning, there is an opportunity. The challenge is figuring out how big that pie is and then how big a slice can be cut out.

I. What are the recognized and unrecognized medical needs?

In any given therapeutic area, there are a host of needs that are both known and unknown. An unmet recognized need could be associated with inadequacies in the current Standard of Care, offering an opportunity that could be addressed through improvements based on specific clinical endpoints. Unrecognized unmet needs can be gleaned through conversations with stakeholders (patients, doctors, payors).

II. How can we best address the unmet needs?

Opportunities can be found on many different sides of the care equation; for example, improved efficacy in terms of ameliorating symptoms or being curative, better safety and tolerability or more convenient forms of dose administration. All these elements factor into better initiation, compliance and adherence. Just because there is a need does not mean there is a viable opportunity. It is critical for companies to clearly define where and how they want to play.

III. Is the science to address the unmet needs differentiated in a clinically relevant way?

Following the characterization of the need is the science. Does the company's science support an improved efficacy, safety or dosing and is it truly differentiated? Over the last decade, the pharma industry has been criticized for developing me-too follow-on compounds designed to stand on the shoulders of patent expiries of blockbuster compounds and offering little in the way of true differentiation. The most powerful advantage in any business, pharmaceutical or otherwise, is the advantage of innovation. For pharma companies, innovation lies in the differentiation of the science.

There has been and will continue to be a tectonic shift from small molecules to large molecules as the science and the solution for disease cure and management becomes increasingly less productive in small molecule development. Scientific developments no longer keep pace with the commercial pressures required for success and growth in the marketplace.

As a result, companies need to carefully assess how their science stacks up in the marketplace versus existing and emerging competition.

IV. Who is the target patient pool?

Of course, there is the patient, who is waiting for relief or a cure. Who are they? How many are there? How many will there be in the future? In assessing target patient populations, product and commercial developers often identify a patient population that is too large, leading to overly-optimistic commercial assessments and possible misappropriation of resources. The key here is to match the medical need with the appropriate patient pool by identifying the underlying symptoms or disease manifestations to as precise a level as possible. An accurate definition and identification of patient populations is critical to many other aspects of commercial development: for example, clinical trials and physician targeting and messaging. The definition also needs to be matched to the clinical profile of the drug. When a company understands the real sub-population for a given indication and the need, it is better able to accurately define the commercial opportunity.

The Market

After defining the market, a company needs to ask itself whether it is going to play in that market, how can it win and who is it going to have to fight with to get its fair share of the market.

V. Who are the prescribers and what do they think?

With a defined patient pool, it is much easier to get a handle on the prescribers and the settings in which they operate. As product development focuses on more targeted indications, understanding the prescribers in terms of who they treat and how they treat is critical to the development of a compound. KOLs are called Key Opinion Leaders for a reason; they help shape and design evolving treatment guidelines. And practicing physicians do what they do best: they practice. Through both qualitative discussions and quantitative surveys with these stakeholders, a company is able to obtain those professional medical practitioner insights that underlie the successful development and ultimate adoption of a given product.

VI. How intense is the competitive intensity?

According to Andrew Grove, former CEO of Intel, only the paranoid survive. This is as true in pharmaceuticals as it is in computer chip-making. In an industry driven by innovation, mass production and evolving needs, the competitive intensity of existing and future markets will either unleash or choke the potential of a given product. What looks good in the current market may look less attractive in the future, given competitive activities.

Like macromolecular crowding, indication opportunities appear and then narrow, depending on the competitive products emerging in a therapeutic space at any given point in time.

This crowding results in opportunities changing in radical ways, and not always for the good. Identification of those emerging market entrants makes an impact analysis necessary for defining the evolving opportunity and assessing how the commercial opportunity could possibly be reduced.

The product landscape of the future needs to be defined in terms of both direct and indirect competition. While it is important to quantify the potential impact and order of entry of competitive pipelines, it is just as important to value the impact of indirect competition, particularly in the treatment algorithm.

For example, what impact could a novel treatment for pre-diabetic patients have in terms of reduction in the patients progressing to diabetes or what happens to second line cancer treatment therapies when a new first line treatment becomes available? Or how do you think about the diagnosis and treatment of a disease when a new test or a new bio-marker shows high degree of correlation?

The continuing emergence of bio-markers and companion diagnostics will also revolutionize the use and the application of assets in development.

As more and more companies focus on personalized medicine, they will seek out and use biomarkers to diagnose disease risk in individual patients and develop appropriate companion diagnostics to assess the safety and efficacy of drugs in specific patient sub-populations.

As ice hockey great Wayne Gretsky said, you have to skate to where the puck is going to be, not where it is.

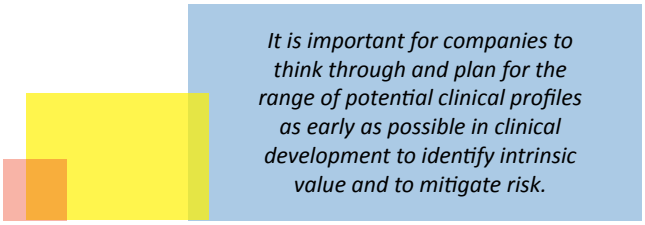
VII. What is the optimal clinical development path and associated regulatory hurdles?

As the market is being defined in terms of patients, prescribers and competitors, just getting the product on the market requires an additional level of analysis. The clinical development path, in terms of defining the market differentiation based on meaningful endpoints, affects acceptance by prescribers and payors as well as regulators. The analysis shapes the delta in endpoints that make or break a product in terms of intent to use as well as intent to prove.

Woody Allen said that 80% of success is just showing up, and the regulatory pathway is the hurdle to just showing up in the medical market space. Increased demands on safety and improved efficacy, as regulators become more conservative and shy away from risk, are significantly reducing the number of drug approvals annually. What is the thought process and guidelines regulators will use? How will the gauntlet of advisory boards be addressed? Defining that shining path becomes an important light at the end of the development tunnel.

Yet just getting regulatory approval is not enough. It is important, starting all the way back in the clinical development process, to target the endpoints that will demonstrate clinically meaningful differentiation.

And what happens if the light grows dim? Clinical development needs to also include contingency options. The various decision paths a drug can follow depends on the outcomes realized at different milestones.



VIII. How do payors, market access, pricing and reimbursement affect the opportunity?

Defining the impact of market access parameters on the target patient pool and the willingness of payors to pay is not always neat nor is it nice. Whether it is the National Institute for Health (NIH) and Clinical Excellence (NICE) in the UK or the various US private and public payors, the payor algorithm needs to be tightly defined and aligned with the treatment algorithm to understand product coverage, acceptance and pricing. How do these payors think? What analogs will provide a guide to that thinking? How do they value the differentiation of the science behind the product and the needs the product is seeking to address?

As if answering these questions wasn't tough enough, pricing goes into a whole new level of complexity. What should the reference price be? What is the relationship between price, formulary status, access and eventually market share? What is the optimal pharmacoeconomic value of a drug? Will some payors demand risk sharing agreements?

These elements of value affect the ability to price in the market and the access available to the target patient pool, depending on reimbursement.

Whether the health system is private insurance as in the US or Government as with the NHS in the UK or different governments in the EU or self-pay in emerging markets, the ability for patients to bear the cost burden is directly and crucially related to the amount of money they have available for treatment. This issue becomes particularly complex in emerging markets where there are large patient populations that rapidly shrink when self-pay is taken into account. In contrast to other kinds of questions where differentiated relationships can be fairly straightforward, payors, access and reimbursement has its own unique set of complexities.

The Value

There are two elements to Value in the SMART questions that you must ask: What are the revenues and how do you mitigate risk and preserve and realize the maximum value?

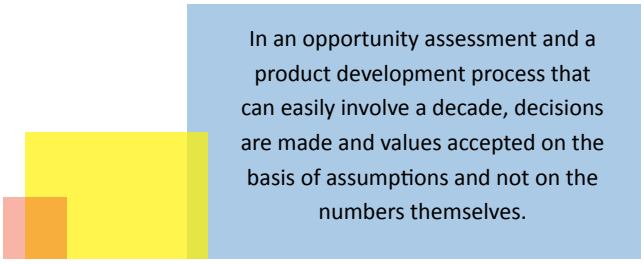
IX. What are the potential revenues associated with this opportunity?

- In developing a revenue forecast, the answers to the questions defined earlier come together to support the financial projections of a given product assessment. This information can be broken up into four key buckets:
- Target Patients (Epidemiology, Diagnosed, Treated, Access)
- Volume (Persistence, Compliance, Dosing)
- Share (Analogs, Attributes, Adoption, Penetration, Cannibalization)
- Game Changers/Event Impact Analysis, e.g. generic entry, new launches

All come together to form the under-pinning of value. Diligent assessment of the questions noted earlier is the only route to a well defined forecast. These estimates can be developed using either a top-down market forecast, which is relatively easy to generate, or a more diligent bottom-up patient based forecast that requires the diligence outlined in the previous key questions.

Once the basic revenue forecast has been generated, further analysis determines the risk adjusted revenue and the risk adjusted net present value (rNPV). Probabilities of success or failure are determined based on the clinical development phase of the modeled compound and probabilities are further adjusted based on the modeled compound's Mechanism of Action (MoA) and targeted therapeutic area. The probabilities generated are applied to the revenue forecast to reflect the risk adjusted revenue.

After this analysis, it is critical to develop a rNPV to ensure that the true value is thoroughly understood inside the organization. Clinical development and operating costs are built in, cash flow streams through the life cycle of the compound are generated utilizing the revenue forecast and cost assumptions and then these streams are risk adjusted for the probabilities of success or failure. These resulting risk adjusted cash flows are finally discounted for the opportunity cost of capital, either company or project specific.



That's why transparency in terms of research and results drive the acceptance of assumptions and the subsequent statement of value.

X. How can risk be managed, value preserved and resources allocated in an optimal way?

Once the value is defined, recognition of risk, optimization of resources, and increase in value begin to define the ongoing process of development. In an ironic byplay of development, pharma companies look to fail earlier and faster to distribute their limited resource allocations behind products that have the best chance of succeeding in the market. At any given point of time, decisions need to be made to defer, expand, contract or abandon a project.

Risk mitigation also involves identifying possible partnerships, options assessments, follow-on products and portfolio synergies – all of which need to be assessed together to preserve individual project and total value for the corporation.

Sometimes, in making investment decisions, low risk projects incorrectly get precedence over "high" risk projects, simply because they appear more achievable. Yet low risk projects rarely break any innovation barriers in the market.

Thus, understanding how to optimize both a given product and a portfolio's development path becomes a crucial element in decision-making.

A key element in this analysis is laying out the clinical development uncertainty measured through asset specific probabilities of technical and regulatory success (PTRS). Unfortunately, pure financial measures penalize early assets due to huge technical and commercial uncertainty, and there is no simple financial measure to directly address this issue. That's why it is important for companies to set optimal goals for what a viable and healthy pharmaceutical portfolio looks like for them taking into account the number of assets by phase of development, balance between high and low risk projects and other factors.

A useful approach to making these kinds of decisions is developing a trade-off analysis among assets to identify optimal optimized portfolio scenarios. This approach is different from stand-alone valuations that are rolled up into a single portfolio of a given value. Instead, the true value of the company's portfolio is optimized by providing an understanding of the effect of asset interdependencies on the total value of the portfolio.

It is also necessary to recognize that these values are ever-changing and dynamic as events happen; thus, portfolio values require consistent monitoring. By adopting this approach, companies can maximize and monitor movements in portfolio value and shareholder return. In so doing, the company can optimize resource allocation across portfolio assets to maximize return and minimize risk for a given level of risk aversion. This approach will also minimize volatility in the portfolio's future value.

The End Game

Now picture the conference room. The projector fan is whirring, throwing more heat into the room, as if all those bodies crowded around the conference table weren't enough. The PowerPoint slide is coming into focus. The General Manager and the Heads of Clinical, Regulatory and that Vice President for Early Commercial Development are waiting with semi-bated breath for the risk-adjusted Net Present Value on a compound that, if it goes forward, will cost $200 million in development and, if the clinical endpoints are met (always the Big-If), will provide a positive return to the corporation and your career. Are these the people you really want to play Truth or Dare with?

But there is no choice. Here come the questions.

The devil, as always, in this game of truth or dare, is hiding in the details. The only way to get at those details is through diligence to find answers to the questions that cut across the issues: Unmet Needs. Differentiated Science. Target Patients. Competition. Pricing. Physicians. Treatment Algorithms. Reimbursement. Value. Risk Management. Portfolio Impact.

By thoroughly identifying these elements in terms of the Opportunity, the Market and the Value, companies can adopt the best industry practices. When Hamlet, one of Shakespeare's ultimate questioners was wondering To be or Not To Be, he desired that it was "a consummation devoutly to be wished." That is what is needed in terms of getting the approvals and then seeing a successful product into the market. Answering those questions and using them to drive product development is the real name of the game. Based on insights developed from critical questions in this commercial game of truth or dare, pharmaceutical and biotech companies can best invest to win.